REMARKS

The Rejection Under 35 U.S.C. § 102 Should be Withdrawn

Claims 1 and 3-7 are rejected under 35 U.S.C. 102 as being anticipated by US 2002/0102302 to Oshlack et al. ("Oshlack"). (Pages 2-3 of the Office Action). Applicants respectfully disagree.

It is well settled that "[a] claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference." *Verdegaal Bros. v. Union Oil Co. of California*, 814 F.2d 628, 631, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987). "The identical invention must be shown in as complete detail as is contained in ... [the] claim." Manual of Patent Examining Procedure (MPEP) § 2131 (8th ed., October 2005); and *Richardson v. Suzuki Motor Co.*, 868 F.2d 1226, 1236, 9 USPQ2d 1913, 1920 (Fed. Cir. 1989).

In particular, the Office Action alleges that Oshlack teaches a sustained release composition (paragraph 0014) comprising:

the double granules of instant claim 1 (paragraph 0023);
the thramadol of instant claim 3 (paragraph 0014);
the fatty acid ester of instant claim 4 (paragraph 0056);
the glyceryl monostearate of instant claim 5 (paragraph 0056);
the acrylic polymer of instant claim 6 (paragraph 0060); and
the additives of instant claim 7(*see* paragraph 0021). Page 3 of the Office Action.

Applicants respectfully traverse the rejection.

Claim 1 of the present application recites sustained-release preparations, which are prepared from double granules obtained (1) by primary granulation of drug according to melt granulation using hydrophobic release-delaying additives, and then (2) by secondary granulation of the obtained granules according to wet granulation using hydrophobic wet-granulation material.

On the contrary, Oshlack relates to a stabilized sustained release oral solid dosage form containing tramadol as an active agent. Oshlack, in paragraph [0023], describes as follows:

"[0023] In embodiments where the hydrophobic material comprises a hydrophilic or hydrophobic polymer in addition to the wax-like substance, the formulation may be prepared by (a) wet granulating the hydrophobic or hydrophilic polymer and optional diluents with or without the tramadol;
(b) drying and sizing the resultant granulate;
(c) combining said tramadol with the granulate if not previously accomplished in step (a); incorporating the wax-like substance in a molten state into the granules using a suitable mixer;
(d) cooling and sizing the granules; and thereafter
(e) optionally lubricating the granules compressing the lubricated granules into tablets. "

Thus, the preparations of Oshlack are different from those of the present invention as shown in the following table.

	Oshlack	The present invention
Primary granulation	Wet granulation	**Melt** granulation
Secondary granulation	Melt granulation	**Wet** granulation

In view of the foregoing, Oshlack fails to teach the essential elements of double granules obtained by (1) primary granulation of drug by melt granulation using hydrophobic release-delaying additives, and then (2) secondary granulation by wet granulation using hydrophobic material, within the claimed invention. Thus, each and every element set forth in the claims is not disclosed in Oshlack. Accordingly, Applicants respectfully request that the rejection under 35 U.S.C. § 102 be withdrawn.

The Claimed Invention is Not Obvious

Claims 1 and 2 are rejected under 35 U.S.C 103(a) as being unpatentable over Oshlack. (Pages 3-4 of the Office Action). It is alleged that Oshlack teaches a sustained release composition (paragraph 0014) comprising a tramadol, hydrophobic material and hydrophobic polymer in concentrations of about 20-80% or 0-80% respectively, and therefore a *prima facie* case of obviousness exists. Office Action, page 4. Applicants respectfully traverse the rejection.

The U.S. Supreme Court has recently addressed the test for obviousness under 35 U.S.C. § 103. (*KSR International Co. v. Teleflex Inc.* 127 S.Ct. 1727, 167 L.Ed.2d 705, 75 USLW 4289, 82 U.S.P.Q.2d 1385 (2007)). In *KSR*, the Supreme Court rejected the Federal Circuit's *rigid* application of the "teaching, suggestion, motivation" test ("the TSM test") in determining obviousness in the particular case in question. (*Id.* at 1739). However, the *KSR* decision indicated that while the TSM test is not the sole method for determining obviousness, it may still be a helpful test. (*Id.* at 1396 ("When it first established [the TSM test], the Court...captured a helpful insight."). Further, the Supreme Court stated it is proper to apply the test set forth in *Graham v. John Deere Co. of Kansas City*, 383 U.S. 1 (1966). (*Id* at 1734). Indeed, in the wake of KSR, the guidelines for the examination of patents clearly state that an Examiner may apply the TSM test following the resolution of the Graham analysis. (*See* Examination Guidelines for Determining Obviousness Under 35 U.S.C. §103 in View of the Supreme Court Decision in KSR International Co. v. Teleflex Inc., 72 Fed. Reg. 57526, 57528 (Oct. 10, 2007) ("USPTO Guidelines")).

The Graham factual inquires, which establish a guide for determining obviousness, are:

(1) determining the scope and contents of the prior art; (2) ascertaining the differences between the prior art and the claims at issue; (3) resolving the level of ordinary skill in the pertinent art; and (4) evaluating any evidence of secondary considerations. (*KSR*, 127 S.Ct. at 1734 (*citing Graham*, 383 U.S. at 15-17)).

Turning to the instant case, Oshlack relates to a stabilized sustained release oral solid dosage form containing tramadol as an active agent. However, Oshlack fails to disclose or suggest the preparations obtained by (1) primary granulation of drug by melt granulation using hydrophobic release-delaying additives, and then (2) secondary granulation by wet granulation using hydrophobic material as recited in claims 1-7. In Oshlack, the formulations are prepared via a melt extrusion/granulation technique. In Oshlack, the invention is to obtain formulations from which active ingredient can be released almost completely after curing process and release rate may be not changed during storage. Thus, Oshlack fails to teach or suggest essential elements of melt granulation and then wet granulation as recited in the present claims.

For example, paragraph [0004] of Oshlack discloses that the agents (e.g., waxes) used in sustained release dosage formulations often present problems of physical stability during storage because they undergo physical alterations on prolonged standing. To solve such problems, in Oshlack, the dosage form is cured at a suitable temperature, until an endpoint is reached at which the cured dosage form, when subjected to in-vitro dissolution, releases the tramadol in amounts which do not vary at any time point along the dissolution curve by more than about 20% of the total amount of tramadol released, when compared to the in-vitro dissolution of the formulation prior to curing. (paragraph [0018] and Claim 1). In all Examples of Oshlack, the preparations are prepared via a melt extrusion/granulation technique, and the purpose is to find the composition from which active ingredient can be released almost completely after curing process and release rate may be not changed during the storage. Therefore, Oshlack does not even teach or suggest any preparations obtained by primary granulation by melt granulation and secondary granulation by wet granulation using hydrophobic material of the present invention.

In view of the foregoing, based upon the disclosure of Oshlack, one ordinary skill in the art would not have been motivated to select the sustained-release preparations for modification to arrive at the instant invention. The PTO has not pointed any teaching that would lead one skilled in the art toward the specific selection of the sustained-release preparations within the instant claims. Applicant respectfully points out that the PTO bears the burden of establishing a case of *prima facie* obviousness against the claims as a whole.

That is, all the claim elements must be considered in a 103 rejection. Accordingly, Applicant respectfully submits that the instant claims are not obvious over Oshlack.

The unexpected results rebut even a *prima facie* case of obviousness

Further, even assuming, *arguendo*, a *prima facie* case of obviousness is established by the cited reference, there is evidence of unexpected or superior results for the sustained-release preparations of the present invention to rebut a *prima facie* case of obviousness. As the Examiner is well aware, such unexpected results can rebut even a *prima facie* case of obviousness. *In re May*, 574 F.2d 1082, 1094 (C.C.P.A. 1978); *see also In re Chupp*, 816 F.2d 643, 646 (Fed. Cir. 1987); *Ortho-McNeil Pharmaceutical v. Mylan Laboratories*, 348 F. Supp. 2d 713, 755 (N.D. W. Va. 2004).

To prove the unexpected results of the present invention over Oshlack, the following experiment was conducted by the inventor (Dr. Joon Ho Bae) and his colleagues at AMOREPACIFIC R&D Center, the assignee of the application. The details are described in the attached Declaration by Dr. Joon Ho Bae.

Table 1: Test preparations

Ingredient (mg)	Preparation of Oshlack 23	Example 13 of the present invention
Tramadol hydrochloride	150	150
Hydrogenated castor oil	150	150
Ethylcellulose	62.2	62.2
Talc	10.2	10.2
Magnesium stearate	7.6	7.6
Total	380	380

Example 13 of the present invention

The primary granules were prepared by melt granulation and then subjected to secondary **wet** granulation. The granules were dried, mixed with talc and magnesium stearate, and compressed to adequate form to prepare tablets.

Preparation of Oshlack

As described in the Declaration by Dr. Joon Ho Bae, the preparation of Oshlack was prepared according to paragraph [0023], which is cited in the Office Action. The primary granule was prepared by wet granulation. Secondary granulation was processed by melt granulation.

Test for effect on surface adhesion

In case of Example 13 of the present invention, adhesion property of the surface of the primary melt granules was covered through secondary **wet** granulation, thus adhesion toward punch or die was not observed during tablet process, while the granules prepared in

Preparation of Oshlack exhibited serious adhesion, as described in the Declaration by Dr. Joon Ho Bae.

Preparation of Oshlack showed serious problems in actual production, *i.e.* reduced flow of particles at hopper, severe adhesion to punch or die at the time of tablet compression and increased resistance at the time of removing tablet from tablet presses, resulting in impossibility of tablet preparation. During tablet process, the adhesion to punch or die induces irregular hole-formation in the surface of the tablet, resulting in a large variation of tablet weight and an irregular drug-release. For sustained-release preparation, the irregular drug-release cannot be accepted because it relates to fatal adverse effect. The adhesion phenomena occur very seriously in the continuous tablet process.

The above test results show that, although secondary granulation is conducted with hydro**phobic** material, in case of secondary **melt** granulation as in Oshlack, adhesion property of the surface of the primary melt granules **cannot** be covered through the second granulation. Only in case of secondary **wet** granulation according to the present invention, adhesion property of the surface of the primary melt granules **can** be covered through second granulation.

In sum, the unexpected effects of the present invention are sufficient to rebut even a *prima facie* case of obviousness. In view of these unexpected results, the instant claims are not obvious. *See In re May*, 574 F.2d at 1094. Therefore, Applicant respectfully requests that the rejection under 35 U.S.C. § 103(a) be withdrawn.

The Double Patenting Rejection Should Be Withdrawn

Claims 1-7 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-13 of copending Application No. 11/572,326. (Office Action, pages 4-5).

Solely to promote prosecution and without prejudice, a terminal disclaimer can be submitted in Application No. 11/572,326 in due course. In any event, Applicants respectfully request that the rejection be held in abeyance until the claims of the present application are deemed otherwise allowable. Thus, Applicants respectfully request that this double patenting rejection be withdrawn.

Conclusion

In view of the foregoing, all the rejections of the claims should be withdrawn. Reconsideration, entry of the above remarks, and allowance of the pending claims are respectfully requested. Should the Examiner not agree that all claims are allowable, a personal or telephonic interview is respectfully requested to discuss any remaining issues and to accelerate the allowance of the above-identified application.

Respectfully submitted,

Date: July 3, 2008

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DECLARATION BY JOON HO BAE, Ph.D. UNDER 37 C.F.R. §1.132

I, Bae, Joon Ho declare as follows:

1. I received my Bachelor of Pharmacy degree in College of Pharmacy from SungKyunKwan University, Suwon, Korea in 1994. I received my MS degree from the Department of Pharmacy at College of Pharmacy from SungKyunKwan University, Suwon, Korea in 1996. I received my PhD degree from the Department of Pharmacy from SungKyunKwan University, Suwon, Korea in 2000.

2. I have been employed by AMOREPACIFIC R&D center of AMOREPACIFIC Corporation, Yonin-si, Gyeonggi-do, Korea, as a Research Scientist from 2000 to 2006, a Senior Research Scientist, a Manager from 2006 to present in the Department of Drug Delivery system.

3. I have published in peer-reviewed journals and made presentations at various industrial and academic conferences of Drug Delivery and Pharmaceutics. I have applied for many patents as a major inventor and co-inventor and some of them are granted and others are pending. I am affiliated with the domestic and international society for Drug delivery and Pharmaceutics, Controlled Release Society (CRS), American Association of Pharmaceutical Scientists (AAPS).

4. By training and experience, I'm familiar with the design of Transdermal dosage form, oral dosage forms, especially oral controlled and sustained release dosage form. I've made a special study of oral controlled release dosage form to optimize drug efficacy and to reduce side effects. Based on formulation and pharmacokinetic study, several advanced oral controlled-release products were successfully lunched in the market.

5. I understand that the pending claim rejection because there was no evidence of superior improvement against Oshlack et al. (US 2002/0102302).

6. To prove superiority of my invention, the following tests were conducted by me and my colleagues at AMOREPACIFIC R&D Center, the assignee of the application.

7. With regard to Oshlack et al. (US 2002/0102302), to prove the unexpected remarkable effect of the present invention, the following experiment was conducted.

7-1. Test preparations

Table 1.

Ingredient (mg)	Preparation Oshlac 23	Example 13 of the present invention
Tramadol hydrochloride	150	150
Hydrogenated castor oil	150	150
Ethylcellulose	62.2	62.2
Talc	10.2	10.2
Magnesium stearate	7.6	7.6
Total	380	380

7-1-(1) Example 13 of the present invention

This preparation is Example 13 of the present invention.

It was prepared according to the method described in the specification of the present invention. A mixture of hydrogenated castor oil and tramadol hydrochloride was heated to 75°C and mixed until hydrogenated castor oil softened. This was cooled to normal temperature to form solid mass; the mass was pulverized and screened with 20 mesh, thereby to prepare primary granules.

The primary granules were mixed with ethylcellulose and subjected to secondary wet granulation. Thus prepared granules were dried, mixed with talc and magnesium stearate, compressed to adequate form to prepare tablets.

7-1-(2). Preparation Oshlac 23

This preparation was prepared according to paragraph 0023 of US 2002/0102302 (Oshlack et al.), which is pointed by the Examiner.

A mixture of ethylcellulose (hydrophobic polymer) and tramadol hydrochloride (75 mg/tablet) was mixed and then the mixture was wet-granulated. After drying, the dried granules were sieved. The passed granules were obtained as primary granules.

The primary granules mixed with hydrogenated castor oil and tramadol hydrochloride (75 mg/tablet). The resultant mixture was heated to 75°C and mixed until hydrogenated castor oil softened for secondary melt granulation. The softened or molten mass was cooled to normal temperature and then sized by sieving with 20 mesh screen. Finally, the passed granules were mixed with talc and magnesium stearate and then the mixture was compressed to form tablets.

7-2. Test for effect on surface adhesion

The primary granules of Oshelac 23 was prepared by wet granulation and the secondary granulation was performed by melt granulation. These granulation processes

were opposite to the process of Example 13.

The resulting preparation of Oschelac 23 still showed adhesion toward punch or die during tablet process because of their waxy and sticky properties. Additionally, preparation Oschelac caused serious problems in actual production, i.e. reduced flow of particles at hopper, severe adhesion to punch or die at the time of tablet compression and increased resistance at the time of removing tablet from tablet presses, resulting in impossibility of tablet preparation. During tablet process, the adhesion to punch or die induces irregular hole-formation in the surface of the tablet thereby to induce a large variation of tablet weight and an irregular drug-release. In case of sustained-release preparation, the irregular drug-release can never be accepted because it relates to fatal adverse effect. The adhesion phenomena occur very seriously in the continuous tablet process.

However, in the case of Example 13, adhesion property of the surface of primary melt granules was covered through secondary wet granulation, thus adhesion toward punch or die was not observed during tablet process.

Based on the above test result, it could be confirmed that, although secondary granulation is conducted with hydrophobic material, in case of secondary **melt** granulation, adhesion property of the surface of the primary melt granules **cannot** be covered through the second granulation. Only in case of secondary **wet** granulation according to the present invention, adhesion property of the surface of the primary melt granules **can** be covered through second granulation.

8. I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like may be punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of any patent issuing from the present application.

Dated: 2008. 6. 20

J. H. BAE

Joon Ho BAE, Ph.D.